REMARKS

Claims 1-30 are all the claims pending in the application. Claims 8, 10, 12-13, 15-17, 19-21, 23 and 27-29 have been amended to correct improper multiple dependencies. The term "water-low" has been changed to "low water" in the specification and the claims to correct an error in translation and for precision of the English language. Hence, no issues of new matter are presented.

Claim Objections

Claims 8-30 were rejected as being in improper. The claims have been amended to eliminate improper multiple dependencies, thus the Examiner's objection is obviated.

Rejections Under 35 USC 112

Claims 1, 3, 13 and 15-16 were rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner stated that the above claims all cite the phrase "water-low soluble" and it is unclear what is meant by this phrase.

As stated above, the phrase water low" has been replace with "low water" to correct an error in translation and for precision of the English language and not for any reason realting to patentability. The phrase "water-low" refers to a substance having low water solubility as opposed to be water insoluble and the use of the term "water-low" was due to an error in

translation. One of ordinary skill in the art would understand that the term "water-low" soluble in the context of Applicants disclosure is synonymous with "low-water" soluble. Hence, Applicant's believe no issues of new matter are presented.

Claim Rejections under 35 U.S.C. § 102

Claims 1, 4-10, 13-19 and 22-27 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent 5,976,573. Specifically, the Examiner states that Kim discloses an aqueous pharmaceutical composition for application to the mucosal surface of the nasal cavity, that includes water, a medicament, a suspending agent comprising microcrystalline cellulose and carboxymethyl cellulose, as well as polysorbate 80. Further, the Examiner refers to column 6, lines 50-57 where it is disclosed that the composition preferably includes an iso-osmotic agent, such as sodium chloride, in order to prevent irritation of the mucosa. Hence, the Examiner concludes that Kim anticipates the limitations of the above-mentioned claims.

Applicant respectfully traverses this rejection on the basis that Kim does not anticipate Applicant's invention as claimed. A prior art reference must teach each limitation of a claim in order to anticipate the claim under 35 USC 102(e). Kim does not teach an aqueous composition having a water insoluble or low water soluble substance, a medicament, and an osmotic pressure less than 290 mOsm as presently claimed. At column. 6, lines 50-57 Kim teaches that an iso-osmotic agent is preferably included in the disclosed composition however, an iso-osmotic

would not provide an osmotic pressure less than 290 mOsm as claimed. Therefore, Kim does not anticipate Applicant's invention.

Claim Rejections under 35 U.S.C. § 103

Claims 1-30 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kim. The Examiner admits that Kim does not teach the inclusion of a hemostatic agent but that no criticality has been placed on the presence of a hemostatic agent in the formulation and it would have been obvious to one of ordinary skill in the art to include a hemostatic agent in a mucosal formulation, to prevent any unwanted bleeding from the surface of the tender mucosal tissue. The Examiner further admits that Kim does not teach all of the examples of Applicants' claimed osmotic controlling agents or water soluble polymers, but, reasons that based on the teachings of Kim, one of ordinary skill in the art would have been motivated to use any osmotic agent, or water soluble polymer, which is known in the pharmaceutical art. Therefore, the Examiner concludes that the present invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant respectfully traverses this rejection based on the fact that Kim does not teach or suggest an aqueous composition comprising a water insoluble or low water soluble substance, a medicament, and having an osmotic pressure less than 290 mOsm. In fact, Kim teaches away from Applicant's invention by suggesting that the disclosed composition preferably include an iso-osmotic agent, which, as discussed above would not provide an osmotic pressure less than

290 mOsm as claimed. Thus, one of ordinary skill in the art would not be motivated to use a water insoluble or low water soluble substance and medicament in an aqueous composition having an osmotic pressure less than 290 mOsm as claimed based upon the teachings of Kim.

Further, the present invention is characterized by the use of osmotic pressure of 290 mOsm or lower to enhance drug uptake of an aqueous pharmaceutical composition which contians a water soluble or water insoluble substance as disclosed by Applicant on page 5, lines 32-page 6, line 3. Kim does not teach or suggest this inventive feature or even recognize the problem with which Applicant is concerned. In view thereof, Kim does not teach or suggest Applicant's invention as a whole.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Applicant hereby petitions for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,

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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims are amended as follows:

1. (Amended) An aqueous pharmaceutical composition for application to the mucosa, comprising one or more water-insoluble and/or ~~water-low~~ low water soluble substance, and one or more medicament, and having an osmotic pressure of less than 290 mOsm.

3. (Amended) An aqueous pharmaceutical composition for application to the mucosa, comprising one or more hemostatic agent, one or more water-insoluble and/or ~~water-low~~ low water soluble substance, and one or more medicament, and having an osmotic pressure of less than 290 mOsm.

8. (Amended) The pharmaceutical composition for application to the mucosa according to claim 1 ~~any of claims 3 to 7~~, further comprising an osmotic pressure-controlling agent.

10. (Amended) The pharmaceutical composition for application to the mucosa according to claim ~~9~~8, wherein said osmotic pressure-controlling agent is sodium chloride.

12. (Amended) The pharmaceutical composition for application to the mucosa according to claim ~~11~~ 8, wherein said osmotic pressure-controlling agent is glucose.

13. (Amended) The pharmaceutical composition for application to the mucosa according to claim 1 ~~any of claims 3 to 12~~, wherein said water-insoluble and/or ~~water-low~~ low water soluble substance is a cellulose.

15. (Amended) The pharmaceutical composition for application to the mucosa according to claim 1 or ~~any of claims 3 to 12~~3, wherein said one or more water-insoluble and/or ~~water-low~~ low water soluble substance is present as solid particles in an aqueous medium.

16. (Amended) The pharmaceutical composition for application to the mucosa according to claim 1 or ~~any of claims 3 to 12~~, wherein said one or more water-insoluble and/or ~~water-low~~ low water soluble substance is dispersed as solid particles in an aqueous medium.

17. (Twice Amended) The pharmaceutical composition for application to the mucosa according to ~~any of claims~~ claim 1 or 3 ~~to 16~~, further comprising a water-soluble polymer substance.

19. (Amended)The pharmaceutical composition for application to the mucosa according to claim ~~18~~17, wherein said water-soluble polymer is carboxymethyl cellulose sodium.

20. (Amended) The pharmaceutical composition for application to the mucosa according to claim ~~1~~8<u>17</u>, wherein said water-soluble polymer is xanthan gum.

21. (Amended) The pharmaceutical composition for application to the mucosa according to claim ~~1~~8<u>17</u>, wherein said water-soluble polymer is hydroxypropyl methyl cellulose.

23. (Twice Amended) The pharmaceutical composition for application to the mucosa according to ~~any of claims~~ claim 1 or 3 ~~to 22~~ , further comprising a surfactant.

25. (Twice Amended) The pharmaceutical composition for application to the mucosa according to any of claims 1 or 3 ~~to 24~~, wherein said medicament is a water-soluble medicament.

26. (Twice Amended) The pharmaceutical composition for application to the mucosa according to any of claims 1 or 3 ~~to 24~~, wherein said medicament is a liposoluble medicament.

27. (Twice Amended) The pharmaceutical composition for application to the mucosa according to ~~any of claims~~<u>claim</u> 1 or 3 ~~to 26~~, wherein said mucosa is nasal mucosa.

28. (Twice Amended) The pharmaceutical composition for application to the mucosa according to ~~any of claims 2 to 27~~ <u>claim 3</u>, wherein said hemostatic agent is one or more selected from the group consisting of tranexamic acid, epsilon aminocaproic acid, carbazochrome,

carbazochrome sulfonate, carbazochrome sodium sulfonate, phytonadione, etamsylate, monoethanol amine oleate, thrombin, hemocoaglase, and adrenochrome monoaminoguanidine mesilate.

29. (Twice Amended) The pharmaceutical composition for application to the mucosa according to ~~any of claims 2 to 28~~ claim 3, wherein the agent other than said hemostatic agent is one or more selected from the group consisting of an antiallergic agent, an antihistamic agent, an anticholinergic agent, a steroid, a vaccine, and a substance for gene therapy, and the mucosa is nasal mucosa.

IN THE SPECIFICATION:

The specification is changed as follows:

Page 1, first paragraph

The present invention relates to a pharmaceutical composition for application to the mucosa to be used in drug therapy comprising a water-insoluble and/or ~~water-low~~low water soluble substance, a medicament, and an aqueous medium, and having an osmotic pressure of less than 290 mOsm. More specifically, the present invention relates to a pharmaceutical composition for application to the mucosa comprising a water-insoluble and/or ~~water-low-~~ low water soluble substance, a medicament, and an aqueous medium, and having an osmotic pressure of less than 290 mOsm, that is superior to conventional pharmaceutical compositions for application to the mucosa, due to efficient and high permeability to the blood at the mucosa.

Page 4, third paragraph

After intensive studies to attain the above first object, the present inventors have found that it is possible to provide a pharmaceutical preparation for application to the mucosa that is superior over conventional liquid composition due to efficient and high permeability through the mucosa to the blood, by formulating a drug that contains a water-insoluble and/or ~~water-low~~low water soluble substance and that has an osmotic pressure of less than 290 mOsm, and thereby have reached the present invention.

Page 4, fourth paragraph

An enhanced absorption of a drug through the mucosa by controlling the osmotic pressure of a pharmaceutical preparation is disclosed in a patent to Ohwaki and has been reported in a paper by Awazu et al. (Pharm. Res. Vol. 10, No. 9, 1372—1377, 1993). However, these phenomena are only observed in aqueous solution preparations that do not contain a water-insoluble and/or ~~water-low~~low water soluble substance, and thereby are essentially different from the pharmaceutical preparation of the present invention in which the inclusion of a water-insoluble and/or ~~water-low-~~ low water soluble substance is essential. Furthermore, it has been shown in Osada's

Page 5, second paragraph

The patent application by Saunders (WO 92-14473) and Helzner (WO 97-01337) described above describe pharmaceutical preparations containing a water-insoluble and/or ~~water-~~

~~low~~low water soluble substance. However, Saunders' patent application (WO 92-11473) makes no description of osmotic pressure of pharmaceutical preparations in general, in its claim, and merely describes in the specification that isotonicity is preferred, and Helzner's patent application makes no description of osmotic pressure of pharmaceutical preparations in general, and merely describes in the specification that the addition of an isotonic agent is preferred. From these patents, therefore, one cannot expect a drastic enhancement in the absorption at low osmotic pressures.

Page 5, second paragraph into page 6

It is surprising therefore that the effect of enhancing drug absorption through the mucosa is drastic when a water-insoluble or ~~water-low~~low water soluble substance is coexistent. That is, although there are reports that the effect of low osmotic pressure is observed in some aqueous solution preparations, we have found, surprisingly, that the effect can be observed by adding a water-insoluble or ~~water-low~~low water soluble substance and the effect does not depend on the type of the drug used.

Page 6, first paragraph

Thus, in the first aspect, the present invention 5 provides an aqueous pharmaceutical composition for application to the mucosa comprising one or more water-insoluble substance and/or ~~water-low~~low water soluble substance and one or more medicament, and having an osmotic pressure of less than 290 mOsm. The composition is a pharmaceutical composition for

application to the mucosa that is superior over conventional pharmaceutical compositions for application to the mucosa, due to markedly efficient and high permeability to the blood at the mucosa.

Page 6, third paragraph

Thus, in the second aspect, the present invention 25 provides a pharmaceutical composition for application to the mucosa comprising one or more hemostatic agent and one or more medicament, and more specifically, an aqueous pharmaceutical composition for application to the mucosa comprising one or more hemostatic agent, one or more water-insoluble substance and/or ~~water-low~~low water soluble substance and one or more medicament, and having an osmotic pressure of less than 290 mOsm. The composition is a pharmaceutical composition for application to the mucosa, that is superior over conventional pharmaceutical compositions for application to the mucosa, due to markedly efficient and high permeability and retentivity at the mucosa.

Page 8, second paragraph into page 9

In the first aspect of the present invention, the water-insoluble and/or ~~water-low~~low water soluble substance is an essential component, and in the second aspect of the present invention, the composition preferably contains a water-insoluble and/or ~~water-low~~low water soluble substance. Such a water-insoluble or ~~water-low~~low water soluble substance may be any substance, and preferred examples include celluloses and more preferably crystalline celluloses.

The concentration of the water-insoluble and/or ~~water-low~~low water soluble substance, that is present as solid particles in an aqueous medium in the first aspect of the present invention, is preferably 0.1% w/w or greater relative to the total amount of the preparation, and more preferably 1% to 10% w/w. The concentration of the water-insoluble and/or ~~water-low~~low water soluble substance that is present as solid particles in an aqueous medium in the second aspect of the present invention is preferably 0.1% w/w or greater relative to the total amount of the preparation, and more preferably 1% to 10% w/w.

Page 9, first paragraph

In any of the aspects of the present invention, preferably the water-insoluble or ~~water-low~~low water soluble substance that is present as solid particles in an aqueous medium is homogeneously dispersed in the aqueous medium.

Page 21, first paragraph

twice as high as that of the pharmaceutical preparation having 290 mOsm or greater (Composition Nos. 11 to 13). It has been also shown that even when isotonic at low osmotic pressure, salts such as sodium chloride (Composition Nos. 2 to 4) have higher bioavailability than water-soluble salts such as glucose (Composition Nos. 5 to 7). Furthermore, it indicates that up to about 1.5%, the higher the concentration of the water-insoluble or ~~water-low~~low water soluble substances is, the higher the bioavailability is (comparison between Composition Nos. 8 and 9 and Composition No.1). Even for the pharmaceutical preparations having a low osmotic

pressure, plasma levels were almost equal to the pharmaceutical preparations having isotonic or high osmotic pressure when they do not contain water-insoluble or ~~water-low~~low water soluble substances (Composition Nos. 14 to 16). These results indicate that the effect of osmotic pressure of the pharmaceutical preparation which is isotonic or lower on the permeability of the ~~water-low~~low water soluble substance to the blood at the mucosa is markedly exhibited only when a water-insoluble or ~~water-low~~low water soluble substance is included, and thereby the effect of the aqueous pharmaceutical composition of the present invention for application to the mucosa was demonstrated.

Page 21, second paragraph into page 22

When the model drug is a water-soluble low molecular weight substance, 5-carboxy fluorescein, plasma levels of 5-carboxy fluorescein in rabbits that were sprayed with a pharmaceutical preparation having a low osmotic pressure of 6 mOsm (Composition No. 17) to the nasal mucosa were markedly higher than those in rabbits that were sprayed with a pharmaceutical preparation having an almost isotonic osmotic pressure of 340 mOsm (Composition Nos. 19) or with a pharmaceutical preparation having a high osmotic pressure of 4000 mOsm (Composition No. 20), and, as shown in Table 3, the bioavailability is increased by 9 to 17 fold. Furthermore, even for the pharmaceutical preparations having a low osmotic pressure, plasma levels were almost equal to the pharmaceutical preparations having isotonic or high osmotic pressure when they do not contain a water-insoluble or ~~water-low~~low water soluble substance (Composition Nos. 21 to 22).

Page 22, first paragraph

These results indicate that the effect of osmotic pressure of the pharmaceutical preparation which is isotonic or lower on the permeability of the ~~water-low-~~ low water soluble substance to the blood at the mucosa is markedly exhibited only when a water-insoluble or ~~water-low~~low water soluble substance is included, and thereby the effect of the aqueous pharmaceutical composition of the present invention for application to the mucosa was demonstrated.

Page 22, third paragraph

Even for the pharmaceutical preparations having a low osmotic pressure, plasma levels were almost equal to the pharmaceutical preparations having isotonic or high osmotic pressure when they do not contain a water-insoluble or ~~water-low~~low water soluble substance (Composition Nos. 27 and 28).

Page 22, fourth paragraph into page 23

These results indicate that the effect of osmotic pressure of the pharmaceutical preparation which is isotonic or lower on the permeability of the ~~water-low~~low water soluble substance to the blood at the mucosa is markedly exhibited only when a water-insoluble or ~~water-low~~low water soluble substance is included, and thereby the effect of the aqueous pharmaceutical composition of the present invention for application to the mucosa was

demonstrated.

Page 23, first paragraph

With regard to the result that compares the absorptivity of fluorescein in Example 1 and Comparative example 1, the relationship between the osmotic pressure and bioavailability is shown in Figure 1. Also, with regard to the result that compares the absorptivity of 5-carboxy fluorescein in Example 2 and Comparative example 2, the relationship between the osmotic pressure and bioavailability is shown in Figure 2. Also, with regard to the result that compares the absorptivity of salmon calcitonin in Example 3 and Comparative example 3, the relationship between the osmotic pressure and bioavailability is shown in Figure 3. It is apparent that in any of the drugs, bioavailability increases with decreased osmotic pressure and that a water-insoluble and/or ~~water-low~~low water soluble substance represented by crystalline cellulose carmellose sodium is required to obtain a high bioavailability.